

### **REMARKS**

Applicants initially wish to thank Examiner Kosack for the telephonic interview conducted on March 19, 2009. During the interview, the outstanding § 112 rejections, claim objections and proposed amendments were discussed. The undersigned attorney also had several subsequent discussions with the Examiner to discuss subject matter that may be eligible for rejoinder and proposed amendments to present a common core structure. Based on the interview and the subsequent discussions, Applicants submit this Amendment and Response.

#### **Amendments to the Specification**

Applicants have amended the specification to place the continuity data in the first line of the specification as requested by the Examiner. More specifically, the present application is a national phase of International (PCT) Application No. PCT/NL03/00804, filed on November 14, 2003, which claims foreign priority benefits under 35 U.S.C. § 365(b) of International (PCT) Application No. PCT/NL02/00732, filed on November 14, 2002.

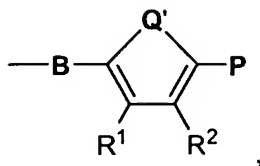
Applicants submit that no new matter is introduced by the the amendments.

#### **Claim Amendments**

Claims 4, 7-51, 53 and 54 are pending. Claims 8-12, 15, 20-30, 35-42, 44 and 50 were withdrawn from further consideration by the Examiner as being drawn to a non-elected invention. Applicants have amended claims 4, 8, 10, 12, 14, 25, 35, 37, 41, 43, and 50; and canceled without prejudice claims 11, 13, 26-30, and 44.

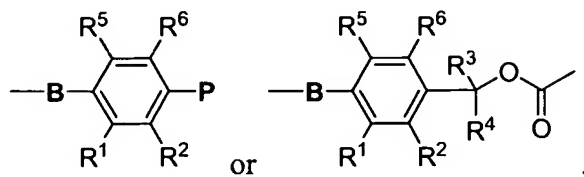
In the Office action dated July 9, 2008, it was stated that “there is no special technical feature that links the inventions together. In chemistry, the special technical feature needs to be a static core structure that is shared by the genus of claimed compounds.”

Applicants have amended claim 4 such that the genus of claimed compounds now shares a common core structure (X-)C. More specifically, X has been amended to have the formula:

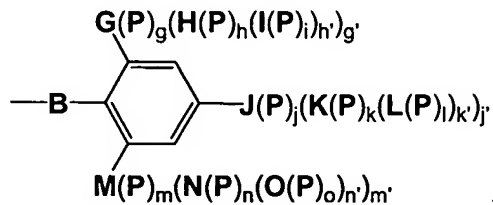


wherein **Q'** is  $-R^5C=CR^6-$ ; **B** is selected from  $NR^7$ , O, and S; **P** is  $C(R^3)(R^4)Q$ ; and **Q** is  $-O-CO-$ .

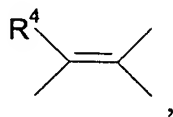
In other words, **X** is



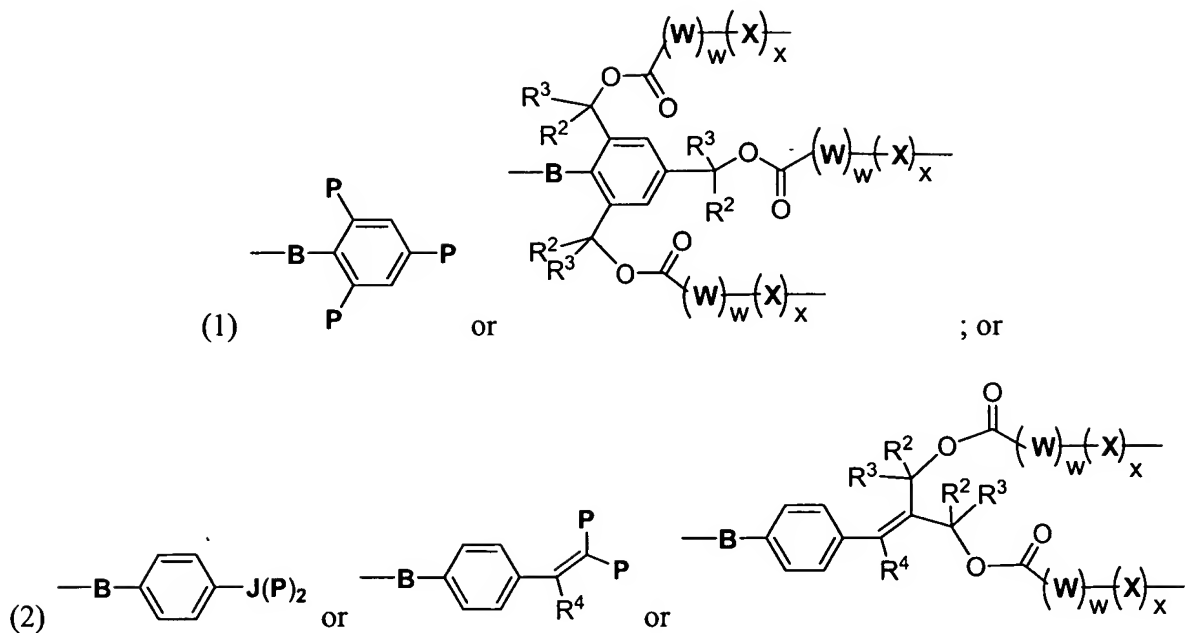
wherein **B** is selected from  $NR^7$ , O, and S; and  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^7$  independently are H or a substituent as recited in claim 4. **C** has been amended to have the formula:



wherein **B** is selected from  $NR^1$ , O, and S; **P** is  $C(R^2)(R^3)Q-(W-)_w(X-)_x$ ; **Q** is  $-O-CO-$ ; **W** and **X** are as defined above; and either (1) **G**, **J**, and **M** independently are **P**, and  $g$ ,  $h$ ,  $i$ ,  $h'$ ,  $g'$ ,  $j$ ,  $k$ ,  $l$ ,  $k'$ ,  $j'$ ,  $m$ ,  $n$ ,  $o$ ,  $n'$ , and  $m'$  all equal 0; or (2) **G** and **M** are hydrogen,  $g$ ,  $h$ ,  $i$ ,  $h'$ ,  $g'$ ,  $m$ ,  $n$ ,  $o$ ,  $n'$ , and  $m'$  all equal 0, **J** is

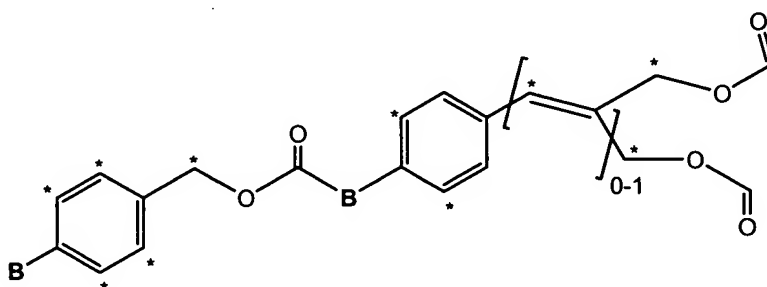


and  $j = 2$  and  $j' = 0$ . In other words, **C** is either:



wherein **B** is selected from  $\text{NR}^1$ , O, and S;  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ , and  $\text{R}^4$  independently are H or a substituent as recited in claim 4; and **W**, **X**, *w*, and *x* are as defined in claim 4.

Accordingly, the genus of claimed compounds recited in amended claim 4 now shares the common core structure (X-)C, where (X-)C can be represented by



wherein **B** is selected from  $\text{NR}^1$ , O, and S, and the carbon atoms marked with an asterisk can have 1-2 optional substituents depending on the valency.

In light of the above amendments and the request for continued examination, Applicants respectfully request that the full scope of amended claim 4 be examined and an expanded search be performed to encompass the core structure (X-)C, where (X-)C is as represented above.

Applicants conducted a structure-based search of the above core structure (X-)C using the CAS

REGISTRY<sup>SM</sup> database, and submit herewith results of the search including copies of those references that date before the filing date of the application, along with other documents and information listed in the Second Supplemental Information Disclosure Statement for the Examiner's consideration.

Applicants submit that the above amendments to the definitions of **W** and **X**, and **C**, **D**, **E**, and **F** are supported by at least original claims 4, 5, 6, 14, and 43.

In addition to the amendments above, Applicants also have amended claim 4 to clarify the definitions of **V** and **A**. Support for the amendments to the definition of **V** can be found in the originally-filed application as published, i.e., U.S. Patent Application Publication No. 2006/0116422, for example, at paragraphs [0140]-[0153]. Support for the amendments to the definition of **A** can be found at least in original claim 11 and in the originally-filed application as published, i.e., U.S. Patent Application Publication No. 2006/0116422, at paragraphs [0125]-[0135].

Further, Applicants have amended claim 8 to replace the term "leaving groups **Z**" with the term "**Z** groups." Claims 10 and 25 are amended to remove non-elected subject matter containing **S**. Claim 12 is amended to make minor editorial changes. Claims 14 and 43 are amended to remove non-elected species that do not contain the core structure (X-)C. Claims 35, 37, 41, and 50 are amended to depend from claim 4 instead of previously canceled claim 1.

Applicants submit that no new matter is introduced by the above amendments.

After entry of this paper, claims 4, 7-10, 12, 14-25, 31-43, 45-51, 53 and 54 will be pending for examination, of which claims 4 and 43 are independent claims.

#### **Rejections Under 35 U.S.C. § 112, First Paragraph**

Claims 4, 7, 13-14, 16-19, 31-34, 45-49 and 51, 53, and 54 stand rejected under the first paragraph of 35 U.S.C. § 112 for allegedly failing to comply with the written description requirement. Specifically, the Office action alleges that the claim limitation "specifiers" as recited in claim 4 was not described in the specification in such a way as to reasonably convey to

one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

Without acquiescing to the rejections but to expedite prosecution, Applicants have amended claim 4 to clarify the definition of V as “an enzymatically removable specifier which is optionally removable after binding to a receptor.”

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (M.P.E.P. § 2163(II)(A)(3)).

Applicants respectfully submit that the specification, in particular the description at paragraphs [0140]-[0153] in the originally-filed application as published, i.e., U.S. Patent Application Publication No. 2006/0116422, describes the genus of “enzymatically removable specifier” in sufficient detail that one skilled in the art can reasonably conclude that the Applicants had possession of the full scope of the claimed invention at the time of filing of the application.

More specifically, at paragraph [0140], Applicants describe that V can be a specifier that typically contains a substrate molecule that can be specifically cleaved by an enzyme present in the vicinity of or insider the target cells. At paragraphs [0141]-[0153], Applicants describe that a specifier V can be formed by reacting various reactive moieties with a nucleophilic group on a protein or protein fragment or a targeting moiety, and provided various examples of reactive moieties, nucleophilic groups, peptides, and targeting moieties.

Applicants submit that the description at paragraphs [0140]-[0153] and the identifying characteristics and examples described therein satisfy the written description requirement for the claimed genus, “enzymatically removable specifier,” and respectfully request reconsideration and withdrawal of the rejections under the first paragraph of 35 U.S.C. § 112.

### **Rejections Under 35 U.S.C. § 112, Second Paragraph**

Claims 4, 7, 13-14, 16-19, 31-34, 45-49 and 51, 53, and 54 stand rejected under the second paragraph of 35 U.S.C. § 112 allegedly as being indefinite for containing the term “leaving group,” which allegedly the specification defines to include a drug.

Without acquiescing to the rejection but to expedite prosecution, Applicants have amended claim 4 to remove the term “leaving group.” As previously presented, the variable Z is defined to be “a therapeutic or diagnostic moiety.”

Applicants respectfully submit that the rejection under the second paragraph of 35 U.S.C. § 112 have been rendered moot.

### **Claim Objections**

Applicants’ claimed invention is directed to compounds that include a specifier V that can be enzymatically removed and that is covalently attached to at least two therapeutic or diagnostic moieties Z via a self-eliminating multiple release spacer or spacer system represented as  $-(W-)_{\text{w}}(X-)C((A-)_{\text{a}})_{\text{c}}$ ,  $-(W-)_{\text{w}}(X-)C(D((A-)_{\text{a}})_{\text{d}})_{\text{c}}$ ,  $-(W-)_{\text{w}}(X-)C(D(E((A-)_{\text{a}})_{\text{e}})_{\text{d}})_{\text{c}}$ , or  $-(W-)_{\text{w}}(X-)C(D(E(F((A-)_{\text{a}})_{\text{f}})_{\text{e}})_{\text{d}})_{\text{c}}$ , where A, C, D, E, F, W, X, a, c, d, e, f, w, and x are as defined in amended independent claim 4. Applicants submit that the claimed compounds all share a common core structure  $(X-)C$ , which is shown on page 33 of this paper.

Claims 4, 7, 13-14, 16-19, 31-34, 43, 45-49, 51, 53, and 54 are objected to for allegedly containing elected and non-elected subject matter.

Applicants have amended claims 10 and 25 to remove non-elected subject matter containing S, and claims 14 and 43 to remove non-elected species that do not contain the core structure  $(X-)C$ .

Based on the above amendments and remarks herein, Applicants respectfully request reconsideration and withdrawal of the claim objections.

### **Rejoinder**

Claims 8-12, 15, 20-30, 35-42, 44, and 50 were withdrawn previously from consideration by the Examiner as being drawn to a non-elected invention. Claims 11, 26-30, and 44 have been canceled without prejudice. Applicants respectfully request that upon allowance of a generic claim, e.g., claim 4, claims 8-10, 12, 15, 20-25, 35-42, and 50 be rejoined for consideration by the Examiner.

### **CONCLUSION**

Based on the above remarks and claim amendments, Applicants believe that the pending claims are in condition for allowance. The Examiner is urged to telephone the undersigned attorney to discuss any remaining issues. Early and favorable action is respectfully solicited.

Respectfully submitted,



Karen K. Chan  
Attorney for Applicants  
K&L Gates LLP  
State Street Financial Center  
One Lincoln Street  
Boston, Massachusetts 02111-2950

Date: June 26, 2009  
Reg. No. L0415

Tel. No.: (617) 261-3215  
Fax No.: (617) 261-3175

BOS-#1314123